

EVALUATION OF METHOTREXATE IN THE MANAGEMENT OF UNDISTURBED TUBAL ECTOPIC PREGNANCY

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ABSTRACT

Background: Ectopic pregnancy is a pregnancy with the zygote implanted outside the endometrium of the uterine cavity. 95% of ectopics are in the tube, 1.5% abdominal, 0.5% ovarian and 0.03% are in the cervix. EP can be diagnosed by serial quantitative beta subunit of human chorionic gonadotrophin hormone and transvaginal ultrasound. Methotrexate injection gives high success rates (86 to 94%) that are not skill-dependent and has become a standard medical treatment in appropriate patients. The best suitable cases for MTX therapy for undisturbed ectopic pregnancy are those who are not suffering symptoms, have a blood level of Q B-hCG of less than 5000 mIU/ml, tubal size less than 3.5 cm, no fetal cardiac activity on US, and will come in to be followed closely. MTX is typically given by injection and this method increases absorption of all of the medicine. Common side effects of MTX treatment for undisturbed EP include: abdominal pain, vaginal bleeding, nausea and vomiting and dizziness. Women diagnosed with an EP were considered candidates for treatment with MTX injection if they were hemodynamically stable, did not have free fluid outside the pelvic cavity on US examination, did not desire surgery and agreed to weekly follow-up visits until the level of serum Q B-hCG was fifty mIU per ml or lower. **Aim of the work:** To evaluate the fate of undisturbed tubal EP after injection of MTX. **Patients and methods:** This prospective study was carried out at the Department of Obstetrics and Gynecology, Zagazig University Hospitals on 54 women with undisturbed EP. The women were informed regarding the treatment and were consented. We gave single dose of MTX (50 mg/m² of body surface area) to the patients. Q B-hCG were followed on day one (injection day), day four and on day seven. We administered 2nd dose of MTX if the level of quantitative of beta subunit on seventh day had not decreased by at least twenty five percent from the first day level and the protocol was repeated. If decrease in quantitative beta subunit between days four and seven was less than fifty percent, a second dose of MTX (50 mg/m²) was given. Weekly measurements were continued until the quantitative beta subunit is undetectable. If quantitative beta subunit falls < fifty percent between weekly measurements after third dose, we perform laparoscopic salpingostomy or salpingectomy. **Results:** In current study the level of Q B-hCG in the studied cases pre-injection ranged from 397 to 7102 mIU/ml, its mean was 4231.9 ± 2210.3. 4th day level ranged from 107 to 7400 and its mean was 3881.7 ± 2317.6 mIU/ml. 7th day level ranged from 30 to 7900 mIU/ml and its mean was 2566.9 ± 2145.6 mIU/ml. The success rate in the current study was 83.3% classified as follows: 44 patients (81.48%) received single dose of MTX. 10 patients (18.52%) received multiple doses one week apart (need prolonged follow up that exceeded 30 days). 6 patients (11.1%) had laparoscopic management and 3 patients (5.6%) had urgent laparotomy. **Conclusion:** There is no pathognomonic pain or findings on examination that are diagnostic for tubal pregnancy. Also the diagnosis of tubal pregnancy, as early as 6-7 weeks postmenstrual by screening of all suspected pregnancies may be the key for optimal use of medical treatment. Transvaginal ultrasound and serial quantitative beta subunit are highly successful in early detection of EP. Medical management by methotrexate injection is safe and cost effective for the resolution of ectopic pregnancy problem.

Key Words: methotrexate, ectopic pregnancy, transvaginal ultrasound.

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INTRODUCTION

There is marked elevation in the incidence of ectopic pregnancy in recent years, to approximately 2% of all pregnancies. The best line of treatment either (invasive, medical or expectant management) is dependent on accurate and early diagnosis of EP. This increases the chance of retaining tubal function^[1].

The main principle has become a conservative approach that helps to save the

tubal function, rather than salpingectomy. Hemorrhage from EP is still the main cause of pregnancy related maternal death in the first trimester and accounts for four to ten percent of all pregnancy related deaths, but improved diagnostic methods leading to earlier detection and treatment^[2].

Methotrexate is an excellent alternative therapy to surgery for special types of EP that carry the greatest risk of haemorrhage such as

cervical, abdominal and cornual ectopic pregnancies^[3].

Methotrexate, which was first described by **Stovall TG** is the most commonly used one because of its simplicity and convenience for both clinician and patient^[4], and decrease the need for surgery and the associated side effects.

Although, there is association with risk of side effects due to injection of MTX, as stomatitis and conjunctivitis, they are usually mild and self-limiting. Thirty percent of patients who receive single-dose management and forty percent of those who receive multi-dose management show side effects^[5]. Also, there is association of failure rate about ten percent to twenty percent for the single-dose therapy and six percent to thirty percent for the multidose therapy and this group of patients requires surgical intervention^[6].

The success of MTX therapy is dependent on the adherence to inclusion criteria. The success rate for single-dose therapy has been reported to be eighty percent to ninety percent and seventy percent to ninety four percent for multi-dose therapy^[7].

the aim of the study is to evaluate the role of mtx in management of undisturbed tubal ectopic pregnancy.

PATIENTS AND METHODS

This interventional cohort study was carried out in the Emergency Unit at the Department of Obstetrics and Gynecology, Zagazig University Hospitals between August 2012 to December 2014 on 54 women diagnosed as undisturbed EP.

All cases were subjected to: full history taking, examination, including general examination, abdominal examination (inspection, palpation, and percussion) and vaginal examination (bimanual examination) if necessary and with caution.

Ultrasound was routinely done for all admitted cases. Most of the US criteria for the diagnosis of EP were fulfilled in the cases of the study. These criteria included:

1. Documentation of the absence of intrauterine pregnancy criteria inspite of high Q B-hCG (higher than 1500 IU/ml).
2. The presence of amorphous material (mostly blood clot) or gestational structures (the yolk

sac or fetal pole) within the dilated fallopian tube.

3. The presence of suspected findings such as tubal ring or its remnants (higher echogenic mass) related to the ovary (relatively of lower echogenicity) and the mass slide separately from the ovary if gently pushed by the vaginal probe.
4. The presence or absence of free fluid in the cul- de-sac which is important in cases of leaking or ruptured tubal pregnancy.

Inclusion criteria:

- Confirmed diagnosis of ectopic pregnancy and feasibility to medical management.
- Transvaginal ultrasound visualization of a gestational sac in the adnexa, with or without fetal pole.
- Absence of cardiac pulsation of the fetus.
- Mass size of EP less than 3.5 cm.
- The woman is hemodynamically stable without signs of hemoperitoneum.
- The woman is able to return for frequent follow-up care or to stay as in patient.
- Normal renal and liver function had been documented within 2 days.
- Normal white blood count and platelet count had been documented as per laboratory standard.
- Normal chest X-ray was obtained if the patient has a history of pulmonary disease.
- No history of allergy or sensitivity to methotrexate or any component of its formulation.

Exclusion criteria:

- Internal haemorrhage and deterioration of general conditions of the patient.
- Signs of impending or ongoing rupture of EP mass, as severe or persistent abdominal pain or presence of more than 300 ml of free peritoneal fluid outside the pelvic cavity.
- Hypersensitivity to MTX.
- Coexistent viable intrauterine pregnancy.
- Breastfeeding.
- Laboratory evidence of immunodeficiency.
- Alcoholism or chronic liver disease.
- The concomitant use of non-steroidal anti-inflammatory drugs.

- Blood dyscrasia such as leukopenia, thrombocytopenia, or severe anemia.
- Active pulmonary disease.
- Hepatic, renal, or hematological dysfunction.
- Adnexal mass ≥ 3.5 cm.
- Presence of cardiac pulsation of the fetus.
- Presence of psychiatric disease such as depression, bipolar disease, psychotic disorder, or drug addiction.
- Women not reliable to comply with study measures and follow up.

Pretreatment testing:

- Q B-hCG, blood type, CBC, renal and liver functions.
- Transvaginal ultrasound.

Precautions done during therapy:

- Avoid vaginal intercourse.
- Avoid PV examinations during follow up of MTX therapy due to risk of rupture of the tube.
- Avoid direct exposure to sun rays to limit risk of skin inflammation caused by MTX.
- Avoid drugs and foods that containing folic acid.
- Avoid administration of NSAIDs as the interaction with MTX may cause suppression of bone marrow, aplastic anemia or GIT toxicity.

Single-dose protocol given to patient:

Before administration of MTX, the patients must be counseled on the risks, benefits, adverse effects, and possibility of failure of MTX treatment, which would lead to rupture of the tube and that need surgical intervention. The patients should be aware of the signs and symptoms associated with rupture of the tube and be advised to ask their doctors with worsening of abdominal pain or tenderness, dizziness, tachycardia, palpitations, or syncope.

Follow up:

Q B-hCG was followed on day one (injection day), day four, on day seven.

We administered a 2nd dose of MTX if concentration of quantitative beta subunit on 7th day had not decreased by at least twenty five percent from level of 1st day and this is repeated.

If decrease in quantitative beta subunit between fourth and seventh day is less than fifteen percent, a second dose of MTX 50 mg/m² was given.

Continuous measurement of quantitative beta subunit is repeated every week until it is become undetectable.

Usually decline to less than 15 mIU/ml we gave maximum 3 doses of MTX.

If falling of quantitative beta subunit Q B- hCG is less than fifteen percent between measurement every weeks after third dose, laparoscopic intervention should be done.

Follow-up was by transvaginal ultrasound, serial Q B-hCG levels and monitoring for side effects of methotrexate.

Women with severe abdominal pain US evaluation for detection of peritoneal fluid is indicated for them.

After MTX therapy, we reported the fate of follow-up as follow:

- Patients respond well to therapy with minimal side effects as stomatitis (dyspepsia and heart burn) and conjunctivitis.
- Patients respond to therapy but with more troublesome side effects as inflammation of GIT, skin, lung, loss of hair, elevation of liver enzymes, and suppression of bone marrow.
- Patients needed laparoscopic management.
- Patients needed urgent laparotomy.

STATISTICAL ANALYSIS

- The results was considered: Significant when the probability of error is less than five percent ($p < 0.05$).
- Non-significant when the probability of error is more than five percent ($p > 0.05$).
- Highly significant when the probability of error is less than zero point one percent ($p < 0.001$).

The smaller the p-value obtained, the more significant are the results.

RESULTS

Table (1) shows that the age group ranged from 20 to 38 years old. Its mean was 27.9 ± 4.5 . The gestational age at diagnosis in the studied cases ranged from 5 to 8 weeks, its mean was 6.4 ± 1.1 .

Table (2) shows that 31 patients (69.8%) had normal vaginal delivery and 13 patients (30.2%) had cesarean section. 37

patients (67.9) had parity ≤ 3 and 17 patients (32.1%) had parity > 4 . 38 (69.8%) patients had no history of abortion while the other 16 patients (30.2%) had positive history of abortion. There are no statistically significant effect of the mode of delivery, parity and abortion on current ectopic pregnancy $P > 0.05$.

Table (3) shows that 50 patients (92.6%) had no history of previous ectopic pregnancy, while the other 4 patients (7.4%) had positive history. 43 patients (79.6%) had no history of pelvic inflammatory disease, while the other 11 patients (20.4%) had positive history. 35 patients (64.2%) did not use intrauterine contraceptive device, while the other 19 patients (35.8%) used it. There are no statistically significant effect of previous ectopic, pelvic inflammatory disease or intrauterine contraceptive device on current ectopic pregnancy $P > 0.05$.

Table (4) shows that there were 35 patients (64.8%) complained of vaginal bleeding, 52 patients (96.3%) complained of pain either lower abdominal pain and tenderness mainly on the affected side, or with cervical movement during vaginal examination or by vaginal probe during transvaginal examination, 50 patients (92.6%) complained of amenorrhea. There are no statistically significant effect $P > 0.05$.

Table (5) shows that the cases who required single methotrexate dose were (44 patients) and who required multiple doses of methotrexate (≥ 2) were (10 patients) as regard pre treatment, 4th day and 7th day level of Q B-hCG. The pre injection level of Q B-hCG in the studied cases ranged from 397 to 7102 mIU/ml, its mean was 4231.9 ± 2210.3 . The 4th day level of Q B-hCG in the studied cases ranged from 107 to 7400 and its mean was 3881.7 ± 2317.6 mIU/ml. The seventh day level of Q B-hCG ranged from 30 to 7900 mIU/ml and its mean 2566.9 ± 2145.6 mIU/ml.

There was non statistically significant difference between patients who required single dose and those who required multiple doses of methotrexate as regard the pre injection Q B-hCG level. P value > 0.05 There was a high statistically significant difference in the 4th day Q B-hCG in patients

who required single dose and those who required multiple doses of methotrexate $P < 0.05$.

Table (6) shows that there were 32 case with adnexal mass size from 0-2cm and success rate of treatment was 100%, while there were 22 case with adnexal mass size more than 2cm out of them 13 case were cured with success rate 59.09%.

Figures (1), (2) and (3) show that There was a statistically significant correlation between US findings and Q B-hCG findings. When the size of the adnexal mass increased in US examination, the level of Q B-hCG was detected to be elevated and vice versa. P value < 0.05 .

Table (7) shows that 43 patients (79.6%) respond well to methotrexate with minimal side effects as conjunctivitis and stomatitis, 2 patients (3.7%) respond well to methotrexate but with rare side effects, the 1st case show epistaxis from thrombocytopenia (platelet count less than 150,000 /cmm), while the 2nd case show persistent cough from pneumonia, 6 patients (11.1%) need laparoscopic management and 3 patients (5.6%) need urgent laparotomy.

Table (8) shows that 44 patients (81.48%) need single dose of methotrexate. 10 patients (18.52%) need multiple doses one week apart a second dose of methotrexate 50 mg/m² was given, the causes of that as the level of quantitative beta subunit was greater than five thousands mIU/mL in 3 cases, the size of the adnexal mass was more than 3cm in other 2 cases, decline in Q B-hCG between day 4 and 7 was less than 15% in the other 5 cases (7 of them need 2 doses and the other 3 cases need 3 doses of methotrexate). 6 patients (11.1%) need laparoscopic management 4 of them due to pain intolerance while the other 2 cases due to failure of medical treatment as Q B-hCG failed $< 15\%$ between weekly measurement after third dose, so laparoscopic salpingostomy or salpingectomy was performed. 3 patients (5.6%) need urgent laparotomy 2 of them were presented with hemodynamic instability, and 1 with acute abdomen with high initial Q B-hCG levels.

Table (1): Demographic data of the studied cases of undisturbed ectopic pregnancy.

	n = 54	p. value	
Age (years)			
Mean ± SD	27.9 ± 4.5	0.42	NS
Range	20-38 Y		
Gestational age at diagnosis			
Mean ± SD	6.7 ± 1.0	0.35	NS
Range	5-8 Ws		

Table (2): Effect of previous mode of delivery, previous abortion and parity on the incidence of ectopic pregnancy.

	N	%	p.value		
Mode of delivery	NVD	31	69.8%	0.57	NS
	CS	13	30.2%		
Parity	1-3	37	67.9%	0.38	NS
	4-7	17	32.1%		
Abortion	-ve	38	69.8%	0.40	NS
	+ve	16	30.2%		

Table (3): Incidence of previous ectopic, previous PID and contraception IUD on incidence of ectopic pregnancy.

	N	%	p.value		
Previous ectopic pregnancy	-ve	50	92.6%	0.20	NS
	+ve	4	7.4%		
History of pelvic inflammatory disease	-ve	43	79.6%	0.59	NS
	+ve	11	20.4%		
Contraception(IUD)	-ve	35	64.2%	0.46	NS
	+ve	19	35.8%		

Table (4):Clinical presentation of the study population.

		N	%	p.value	
Vaginal bleeding	-ve	18	35.2%	0.47	NS
	+ve	35	64.8%		
Abdominal pain and tenderness	-ve	2	3.7%	0.13	NS
	+ve	52	96.3%		
Amenorrhea	-ve	4	7.4%	0.11	NS
	+ve	50	92.6%		

Table (5): Comparison between the cases who required single methotrexate dose and who required multiple doses of methotrexate as regard pre treatment, 4th day and 7th day level of Q B-hCG.

	Single dose (resolved group) (n =44)	Multiple dose (≥ 2 doses) (n = 10)	T	P
Pre				
Mean ± SD	4231.9 ±2210.3	5626 ±1417.7	1.89	> 0.05
Range	397-7102	3430-7200		
4th				
Mean ± SD	3881.7 ± 2317.6	6230.5 ± 1063.7	3.11	< 0.001
Range	107-7400	4005-7800		
7th				
Mean ± SD	2566.9 ± 2145.6	6189.0 ± 1192.3	5.13	< 0.001

Table(6):Ultrasound adnexal mass size correlated to success of treatment. The mass ranged from 8 to 32 mm, the mean was 23.3 ± 7.2.

Adnexal mass (cm)	Successful	
	No	%
0-2 (n = 32)	32	100%
> 2 (n = 22)	13	59.09%

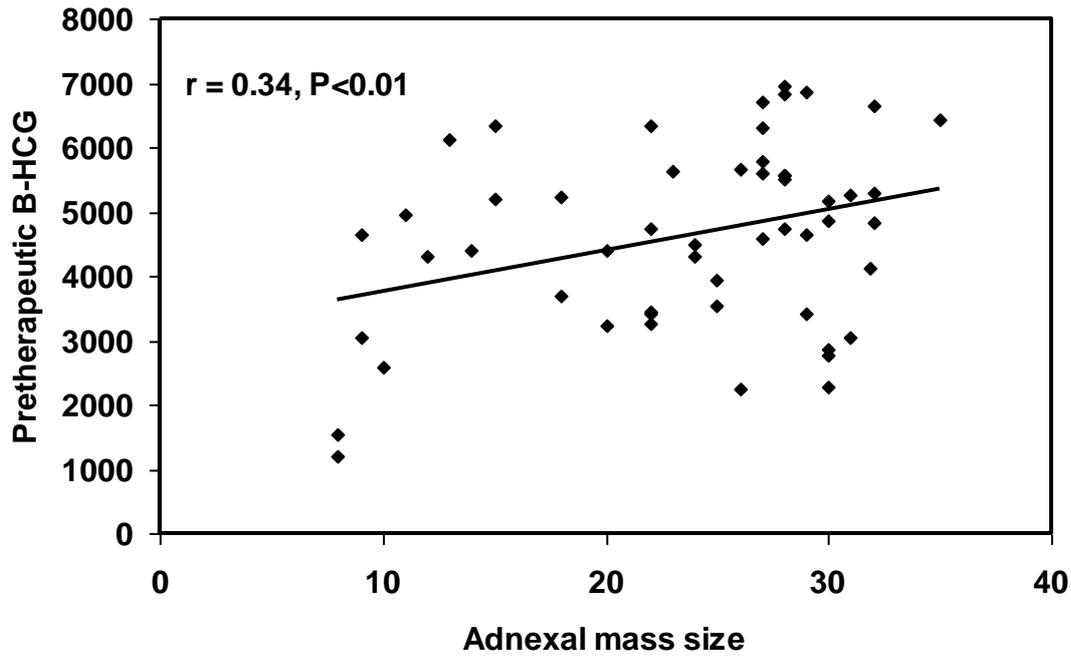


Fig. (1): Significant correlation between the adnexal mass size and the pretherapeutic Q B-hcG.

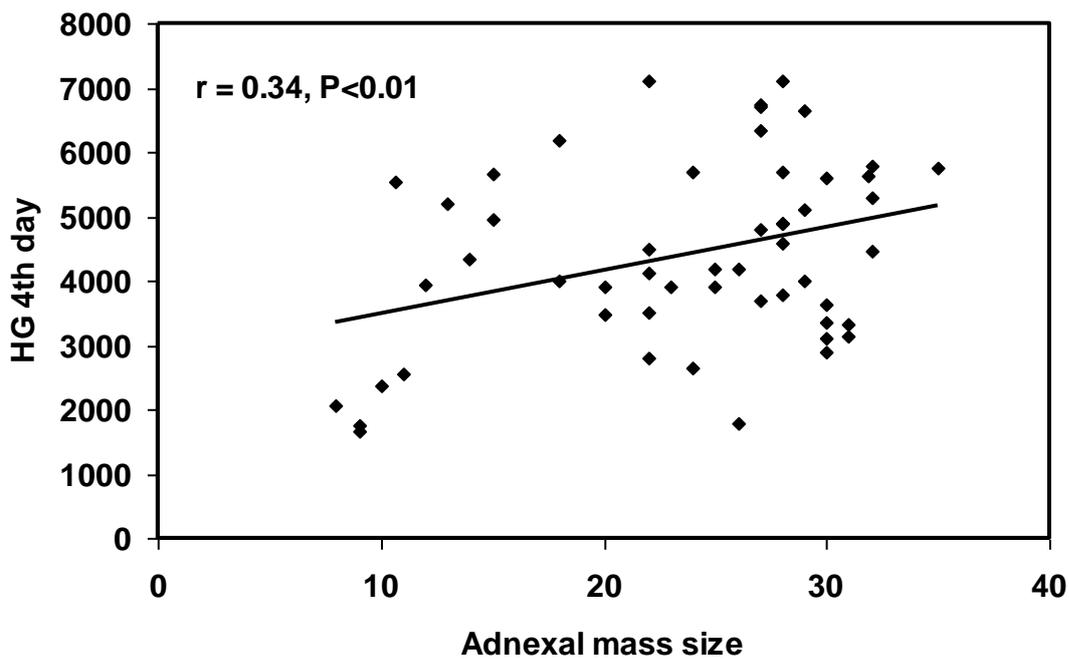


Fig. (2): Significant correlation between the adnexal mass size and the Q B-hcG in the fourth day of medical treatment.

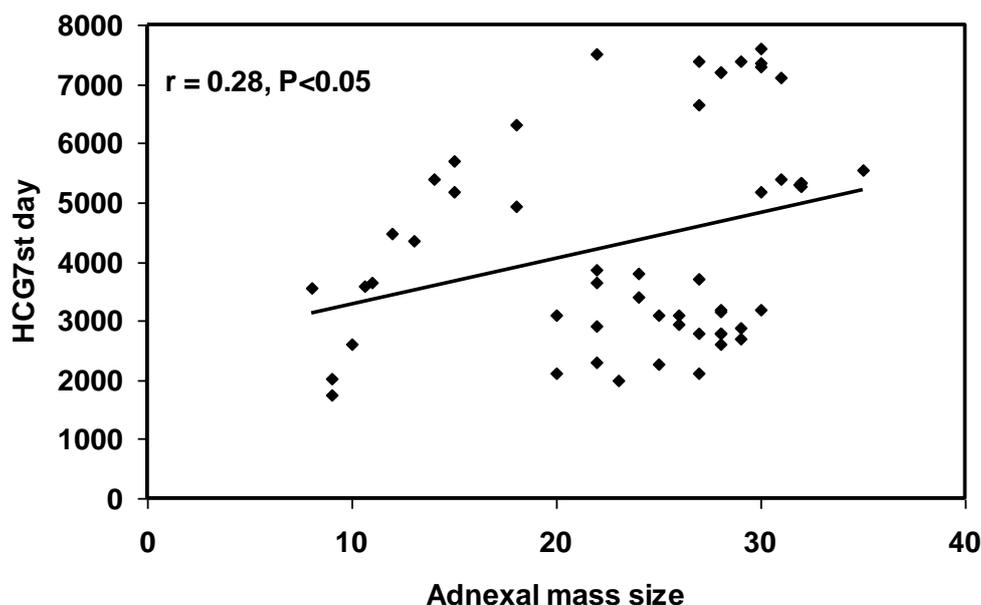


Fig. (3): Significant correlation between the adnexal mass size and the Q B-hcG in the seventh day of medical treatment by methotrexate.

Table (7): Response to methotrexate treatment in the study population.

	No	%
Patients respond well to therapy with minimal side effects	43	79.6
Patients respond with some side effects	2	3.7
Patients need laparoscopic management	6	11.1
Patients need urgent laparotomy	3	5.6

Table (8): Mode of treatment of undisturbed ectopic pregnancy in the study population.

Mode of treatment	N	%
Methotrexate		
Single dose	44	81.48
Multiple dose	10	18.52
Patient need laparoscopy		
-ve	48	88.88
+ve	6	11.12
Patient need laparotomy		
-ve	51	94.44
+ve	3	5.56

DISCUSSION

This study was carried out in outpatient clinic of Zagazig University Maternity Hospital between August 2012 to December 2014. The study included 54 pregnant patients with undisturbed ectopic pregnancy at time of presentation who were managed by conservative medical treatment with methotrexate.

The aim of this study was to evaluate the role of conservative medical treatment of undisturbed ectopic pregnancy with methotrexate .

In this study the clinical presentation of pregnant patients may be by vaginal bleeding that presented in 35 patients(64.8%) or lower abdominal pain presented in 52patients(97.3%) or amenorrhea presented in 50 patients(92.6%).

Fletche Elson J et al.⁽⁸⁾ stated that pain and bleeding may occur together in about 1/3 of patient with ectopic pregnancy.

In this study, 15 patients (27.8 %) had risk factors of ectopic pregnancy either due to previous ectopic (4 patients 7.4 %) or symptoms of PID (11 patients 20.3%) This was found to be in accordance with **Shaw JL, Dey SK, et al.**⁽⁹⁾ who revealed that risk of ectopic pregnancy increases approximately 3 folds for women with documented tubal pathology.

In this study, 19 patients (35.8 %) used IUD which was removed on diagnosis of ectopic pregnancy. Previous exposure to abdominal or pelvic surgery was recorded in 13 patients(24.1) as previous CS or previous abortion that recorded in 16 patients(29.6).

Gamzu R, Almog B, Levin Y et al.⁽¹⁰⁾ demonstrated the success with the single-dose regimen to be 88.1%, while the success with the multiple dose regimen was 92.7%.

In this study, 44 patients (81.48%) need single dose of methotrexate ,10 patients (18.52%) need multiple doses one week a part.

In this study there was no statistical significant difference as regard the mean size of adnexal mass as there were 32 case with adnexal mass size from 0-2cm and success rate of treatment was 100% ,while there were 22 case with adnexal mass size more than

2cm out of them 13 case were cured with success rate 59.09%.

Hopkisson J. et al.⁽¹¹⁾ also demonstrated the single-dose regimen to have a slightly higher failure rate.

In the current study it was found that ectopic pregnancy was resolved by methotrexate treatment in 45 patients (83.3%) and the remaining 9 patients (16.7%) needed surgical interference 6 patients (11.1%) need laparoscopic management 4 of them due to pain intolerance while the other 2 cases due to failure of medical treatment as Q B-hCG failed < 15% between weekly measurement after third dose, so laparoscopic salpingostomy or salpingectomy was performed, 3 patients (5.6%) need urgent laparotomy 2 of them were presented with hemodynamic instability, and 1 with acute abdomen with high initial Q B-hCG levels.

- **Mol F, van den Boogaard E, van Mello Nm, et al.**⁽¹²⁾ stated that reported success rates of single dose methotrexate range 65 to 95%.

In current study, there was a statistical significant lower mean Q B-hCG level in resolved group when compared to surgical group at 4th and 7th day of follow up P<0.05. On the 4th day, there was statistical significant lower Q B-hCG level with a mean level of 3881.7 ± 2317.6 mIU/ml lower than the pretreatment Q B-hCG in resolved group . On the 7th day, there was statistical significant decrease in Q B-hCG level and its mean was 2566.9 ± 2145.6 mIU/ml in resolved group.

In surgical group, there were no statistical significant changes between Q B-hCG level at 4th day and after 7th day.

To do comparison between our study and other studies the success rate in other studies was found to be more than in our study, this due to the beginning of starting the MTX injection in our studied populations with increasing quantitative beta subunit values and complaints of abdominal pain were taken early for surgical intervention for fear of rupture of the EP. With more experience of using the drug, the success rate will be increased .

Accurate detection of cases and strict selection to the inclusion criteria of low

quantitative beta subunit levels, size of adnexal mass is less than 3.5 cm and good clinical procedures avoided early surgical intervention and improvement of the success rate is year by year(13).

Srivichai K et al.⁽¹⁴⁾ reported a success rate of ninety point six percent in ninety six out of one hundred and six patients were successfully treated with MTX though 4 of them need a 2nd dose. Success reached ninety percent (n = 10) in patients out of eleven with single dose treatment.

Merisio et al.⁽¹⁵⁾ Failure of MTX treatment is due to a high increase in quantitative beta subunit level from 4th to 7th day after injection.

There is marked increase in size of EP and may persist for weeks on serial US examinations after injection, this may be represents hematoma formation rather than persistent trophoblastic tissue, and is not prediction of medical treatment failure. Also increase in quantitative beta subunit levels in three days following medical treatment (up to 4th day) this may be due to continuous production of human chorionic gonadotrophin hormone by syncytiotrophoblast despite cessation of production by cytotrophoblast(16).

Sensation of pain after MTX treatment may be due to abortion through the tube or hematoma formation that cause stretch of the tube that may contribute with tubal rupture and failure of medical therapy⁽¹⁷⁾.

Fearing of tubal rupture misleads clinicians to do early surgical intervention on unruptured EP that may be resolve with medical MTX therapy.

It is difficult to differentiate between separation pain due to tubal abortion from pain due to tubal rupture and this may lead to early surgical intervention(18).

Mamdoh⁽¹⁹⁾ demonstrated that quantitative beta subunit of two thousands mIU/ml is an optimum value for selecting cases for medical failure using the single dose approach as cases with initial quantitative beta subunit value of more than two thousands mIU/ml and/or in embryonic sac is more than three point four cm should be closely monitored for failure of medical treatment.

MTX regimen with multiple dose for haemodynamically stable women with an

unruptured tubal EP with serum quantitative beta subunit concentrations less than three thousands mIU/ml and a single-dose of MTX for serum quantitative beta subunit less than one thousand and five hundreds mIU/ml is recommended. Women with a pretreatment quantitative beta subunit level of three thousands to four thousands mIU/ml have more probability of surgical intervention or multiple dose treatment⁽²⁰⁾.

Persistent of EP after laparotomy with conservation of the tube was three to five percent and after laparoscopy was three to twenty percent. Administration of MTX decrease the incidence of persistent trophoblast. Persistent trophoblast is detected by the failure of serum quantitative beta subunit levels to fall as expected after initial treatment, often a problem occurring after salpingotomy rather than salpingectomy⁽²¹⁾.

CONCLUSION

From the current study we concluded that there is no pathognomonic pain or findings on examination that are diagnostic for tubal pregnancy. Also the diagnosis of tubal pregnancy, as early as 6-7 weeks postmenstrual by screening of all suspected pregnancies may be the key for optimal use of medical treatment.

TVUS and serial quantitative beta subunit are highly successful in early detection of EP.

The treatment of ectopic pregnancy, no longer necessarily requires laparotomy or laparoscopic management. Medical management by methotrexate injection is safe approach for the resolution of ectopic pregnancy problem.

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